Contains Nonbinding Recommendations

Draft Guidance on Buprenorphine Hydrochloride; Naloxone Hydrochloride

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Buprenorphine hydrochloride; Naloxone hydrochloride

Dosage Form; Route: Sublingual tablet; oral

Recommended Studies: One study

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 5.7 mg base/EQ 1.4 mg base
   Subjects: Healthy males and nonpregnant females, general population, aged 18 to 50 years
   Additional comments:
   a) Tablet should be placed under the tongue until completely dissolved; tablet should not be moved after placement. Advise subjects not to chew or swallow the tablet.
   b) Exclude subjects who have received any opioid within 14 days of dosing.
   c) An opioid antagonist, such as naltrexone hydrochloride oral tablet, 50 mg, should be used to minimize opioid-related adverse events. The opioid antagonist should be administered well in advance of dosing, in order to achieve adequate blockade of opioid receptors. Please consult with a physician who is an expert in the administration of opioids for the appropriate dose and dosing regimen of an opioid antagonist for a single dose of buprenorphine hydrochloride and naloxone hydrochloride sublingual tablet EQ 5.7 mg base/EQ 1.4 mg base administered to a healthy volunteer who had not received any opioid within 14 days of dosing.
   d) A clear plan for continuous respiratory monitoring from the time of dosing past the time of expected peak effect of the drug (i.e., at least 3 hours after dosing) should be included. Standard operating procedures (SOPs) should be in place for assessing and treating ventilatory depression, and personnel qualified to treat ventilatory emergencies should be immediately available.
   e) Buprenorphine hydrochloride and naloxone hydrochloride sublingual tablet is under a Risk Evaluation and Mitigation Strategy (REMS) program with Elements to Assure Safe Use (ETASU) (1) to mitigate the risks of accidental overdose misuse and abuse and (2) to inform patients of the serious risks associated with this drug product. All pertinent elements of this REMS and of the warnings in the approved labeling for buprenorphine hydrochloride and naloxone hydrochloride sublingual tablet must be incorporated into the protocol and informed consent in the bioequivalence study.

Analytes to measure (in appropriate biological fluid): Buprenorphine and its active metabolite, norbuprenorphine, in plasma. For naloxone, measure unconjugated and total naloxone in plasma.

Submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}.

Bioequivalence based on (90% CI): Buprenorphine and naloxone

Waiver request of in vivo testing: EQ 1.4 mg/0.36 mg base strength based on (i) acceptable bioequivalence study on the EQ 5.7 mg/1.4 mg base strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths. Refer to the Mirtazapine Tablet Draft Guidance for additional information regarding waivers of in vivo testing.

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website available to the public at the following location: http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).